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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/177,387	10/23/98	HARTLEY J	0942.2850004

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EXAMINER	
YUCEL, I	

ART UNIT	PAPER NUMBER
1636	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

please see attached

Office Action Summary	Application No. 09/177,387	Applicant(s) Hartley et al.
	Examiner Remy Yucel	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Apr 15, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *26-35* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *26-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 & 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 26-35 are pending in the application.

This Office action is in response to the communication filed 15 April 1999.

Election/Restriction

Applicant's election without traverse of group II (claims 26-35) in Paper No. 6, filed 15 April 1999 is acknowledged.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26-29 and 31-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Bebee *et al.* (A).

The instant claims are drawn to methods of modifying nucleic acids to include or incorporate specific recognition sites for recombination enzymes via polymerase chain reaction-based methods.

Bebee *et al.* teach cloning of nucleic acids (DNA) by taking advantage of the Cre recombinase system. They teach the sequences for the specific lox P sites recognized by the Cre enzyme (see for example column 5). They also teach PCR primers #790 and #791 which include the LoxP recombination sites and the amplification of a kanamycin resistance gene from a plasmid with said primers. They teach that as a result of PCR, a "cassette" or fragment comprising the kanamycin resistance gene flanked by loxP sites is obtained (see for example, columns 11 and 12). They further teach that this product (cassette) was ligated into another construct, indicating that as a result of PCR amplification, a double-stranded product was obtained. Bebee *et al.* do not specifically disclose specific thermostable DNA polymerases used in their PCR reactions; however, the list recited in claim 33 is fairly complete and recites some of the first commercially available enzymes such as Taq, VENT and DEEPVENT. That Bebee *et al.* did not specify the polymerase used in their PCR reaction indicates that any DNA polymerase suitable for PCR would be appropriate in their methods and that by the time of their invention, PCR protocols were well known and established to the point that one of ordinary skill in the art would have recognized and known appropriate DNA polymerases (thus Bebee *et al.* did not disclose that which was well known). Therefore, Bebee *et al.* teach that which is recited by the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilby *et al.* (U), Snaith *et al.* (V) or Hartley *et al.* (B) in view of Ausubel *et al.* (W) and further in view of Padgett *et al.* (X) or Grose *et al.* (C).

Claims 26-29 and 31-35 have been described above. Claim 30 is drawn to methods of modifying nucleic acids to include or incorporate specific recognition sites for recombination enzymes via polymerase chain reaction-based methods wherein the nucleic acid is RNA.

The first three references are cited because they illustrate that it was known and recognized in the art that site specific recombination facilitates cloning and engineering of nucleic acids. Kilby *et al.* present an overview of site specific recombination systems and their potential

uses for engineering of genomes. They present the sequences for specific recombination sites from the Cre/lox and the FLP/FRT systems.

Snaith *et al.* also teach the importance of the site specific recombination systems for manipulation of target nucleic acid molecules. They teach plasmids with loxP and FRT recognitions sites in their multiple cloning sites to facilitate the construction of (target) molecules for recombination. They, too, disclose the sequences for the recognition sites for both systems.

Hartley *et al.* teach recombinational cloning using engineered site specific recombination sites. At column 17 they teach a nucleic acid molecule having at least two engineered recombination sites flanking a gene of interest or desired segment. They teach plasmids that allow the generation of the gene of interest or desired segment that is flanked by the recombination sites.

None of the references above disclose the introduction of recombination sites via a PCR based method. The reference either do not disclose how the sites are incorporated or they disclose other, equivalent methods such as cloning and ligating fragments with the appropriate sites to the molecules of choice.

Ausubel *et al.* teach various PCR-based methods for introducing modifications (any desired sequence change) to nucleic acids (see 8.5.1). They teach PCR methods in which a desired restriction site is incorporated into a desired nucleic acid using appropriate primers and Taq polymerase.

Padgett *et al.* and Grose *et al.* are cited to illustrate that the methods taught by Ausubel *et al.* function to incorporate any desired sequence into any nucleic acid. Padgett *et al.* teach PCR methods to incorporate a specific recognition site for a specific enzyme, Eam1104I. They teach the introduction of their sites at or near the termini of their fragments using appropriate primers and Taq polymerase.

Grose *et al.* teach a recombination site specific PCR mutagenesis technique in which a specific stretch of 24 nucleotides were inserted into a gene using "mutating primers" (see for example column 3). Grose *et al.* teach the incorporation of a specific tag into a nucleic acid of interest (see for example columns 7-9, 13 and 14), further illustrating that, at the time of the invention, it was well known to use PCR-based methods to incorporate desired sequences (for example, recognition sites or tags) into specific locations of target nucleic acid molecules of interest.

Given the teachings of the prior art discussed immediately above, the ordinary artisan would have been motivated to incorporate recombinase recognition sequences into a nucleic acid of interest (DNA or RNA) because of the teachings of Kilby *et al.*, Snaith *et al.* or Hartley *et al.* who teach the advantages of site specific recombination systems for molecular engineering (cloning). The ordinary artisan would have been further motivated to use PCR-based techniques taught by Ausubel *et al.* and exemplified by Padgett *et al.* and Grose *et al.* for introducing the recognition sites of interest. Ausubel *et al.* teach that any sequence may be introduced via PCR methods, including restriction sites. This teaching, as well as the demonstration of Padgett *et al.*,

speaks directly to the crux of the claimed invention--which is the introduction of recognition sites for recombinase enzymes into a nucleic acid. Restriction sites, which are recognition sites for restriction enzymes, are analogous to the recognition sites for the recombinase enzymes of the instant invention. The ordinary artisan would have been motivated to use PCR-based methods for the introduction of the sites because of the teachings of Ausubel *et al.* The ordinary artisan would have also recognized that, by using PCR-based methods for said introduction, the recognition sites for the recombinase enzymes could be inserted at precise locations of the nucleic acid molecule, independent of the presence of appropriate restriction sites for cloning. The ordinary artisan would have an expectation of success of using PCR-based methods for incorporation of specific (recombination sites) sequences (as taught by Kilby *et al.*, Snaith *et al.* or Hartley *et al.*) because of the teachings of Padgett *et al.* and Grose *et al.* who demonstrate incorporation of desired sequences as per the teachings of Ausubel *et al.* Thus, the invention, as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

Claim rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-30, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations "said synthesized molecule" and "said synthesized double stranded nucleic acid molecule" in claims 27 and 28, respectively, lack antecedent basis.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what the distinction is between mRNA and poly A RNA; it appears that the recitation "poly A RNA" is redundant.

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "and mutants, variants and derivatives thereof" renders the claims indefinite because the metes and bounds of the claim cannot be established. The use of "brand name" polymerases in the claim indicates that Applicant is referring to a specific polymerase. However, it is not clear what enzymes are encompassed by the recitation "and mutants, variants and derivatives thereof."

Further "derivation" connotates that the enzymes are changed as a result of chemical manipulation, in which case the claims would read on many different versions of the same protein; however, it is unclear as to what type of derivative processes are covered by this recitation. again, rendering the metes and bounds of the claims indefinite. Because the nature and number of the derivative processes are not disclosed, it is not clear which mutants, variants and derivatives are to be included. It is further not clear what, if any, the distinction(s) are among the terms "mutants", "variants" and "derivatives".

Conclusion

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6 (d)). The Group 1800 FAX numbers are (703) 308-4242 or (703) 305-3014. Unofficial faxes may be sent to the examiner at (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Remy Yucel, Ph. D. whose telephone number is (703) 305-1998. The examiner can normally be reached on Monday through Fridays from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Remy Yucel

REMY YUCEL, PH.D
PATENT EXAMINER

June 21, 1999